10/682,584

4/3/07

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FILE 'HOME' ENTERED AT 13:23:36 ON 03 APR 2007

=> file registry
COST IN U.S. DOLLARS                                 SINCE FILE      TOTAL
                                                          ENTRY    SESSION
FULL ESTIMATED COST                                        0.21       0.21

FILE 'REGISTRY' ENTERED AT 13:23:49 ON 03 APR 2007
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DICTIONARY FILE UPDATES:    2 APR 2007  HIGHEST RN 928880-35-7

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http://www.cas.org/ONLINE/UG/regprops.html

=> s "cyclopamine"
L1            6 "CYCLOPAMINE"

=> file medline, caplus, wpids, uspatfull
COST IN U.S. DOLLARS                                 SINCE FILE      TOTAL
                                                          ENTRY    SESSION
FULL ESTIMATED COST                                        5.40       5.61

FILE 'MEDLINE' ENTERED AT 13:24:26 ON 03 APR 2007

FILE 'CAPLUS' ENTERED AT 13:24:26 ON 03 APR 2007
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FILE 'USPATFULL' ENTERED AT 13:24:26 ON 03 APR 2007
CA INDEXING COPYRIGHT (C) 2007 AMERICAN CHEMICAL SOCIETY (ACS)

=> s l1 and ("differentiation" or "apoptosis")
L2          154 L1 AND ("DIFFERENTIATION" OR "APOPTOSIS")

=> s l2 not py>2001
L3            9 L2 NOT PY>2001

=> d l3 1-9 ibib, abs, hitstr
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L3   ANSWER 1 OF 9     MEDLINE on STN
ACCESSION NUMBER:    2001441541     MEDLINE  Full-text
DOCUMENT NUMBER:     PubMed ID: 11487541
TITLE:               Sonic hedgehog regulates gastric gland morphogenesis in man
                     and mouse.
AUTHOR:              van den Brink G R; Hardwick J C; Tytgat G N; Brink M A; Ten
                     Kate F J; Van Deventer S J; Peppelenbosch M P
CORPORATE SOURCE:    Department of Experimental Internal Medicine, Academic
                     Medical Center, Meibergdreef 9, 1105 AZ Amsterdam, The
                     Netherlands.. g.r.vandenbrink@amc.uva.nl
SOURCE:              Gastroenterology, (2001 Aug) Vol. 121, No. 2, pp. 317-28.
                     Journal code: 0374630. ISSN: 0016-5085.
PUB. COUNTRY:        United States
DOCUMENT TYPE:       Journal; Article; (JOURNAL ARTICLE)
LANGUAGE:            English
FILE SEGMENT:        Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH:         200108
ENTRY DATE:          Entered STN: 13 Aug 2001
                     Last Updated on STN: 3 Sep 2001
                     Entered Medline: 30 Aug 2001
AB    BACKGROUND & AIMS: Gastric epithelial renewal is an asymmetric process.  A
      stem cell located halfway up the tubular unit gives rise to both a basal gland
      region and a luminal pit compartment, but the mechanisms responsible for the
      maintenance of this asymmetry are obscure.  We investigated whether Sonic
      hedgehog (Shh), an established polarizing signal protein during development,
      is expressed and functional in the adult human and murine stomach.  METHODS:
      Expression of Shh and putative transcriptional targets was investigated using
      immunoblot and immunohistochemistry.  Mice were treated with the Shh inhibitor
      cyclopamine and examined for expression levels of Shh targets and
      proliferation of gastric epithelial cells.  RESULTS: Shh was expressed in the
      stomach.  In cyclopamine-treated mice, we observed decreased expression of
      HNF3beta, Islet (Isl)-1 and BMP4, 3 putative Shh target genes.  Inhibition of
      Shh markedly enhanced gastric epithelial proliferation and affected the cell
      cycle of gastric epithelial gland cells, whereas pit cells remained
      unaffected. CONCLUSIONS: Shh controls the expression of at least 3 factors
      important for epithelial differentiation and is a negative regulator of
      gastric gland cell proliferation.  Shh is a candidate polarizing signal in the
      maintenance of gastric pit-gland asymmetry.


L3   ANSWER 2 OF 9     MEDLINE on STN
ACCESSION NUMBER:    2001059467     MEDLINE  Full-text
DOCUMENT NUMBER:     PubMed ID: 11042037
TITLE:               Erythroid differentiation in vitro is blocked by
                     cyclopamine, an inhibitor of hedgehog signaling.
AUTHOR:              Detmer K; Walker A N; Jenkins T M; Steele T A; Dannawi H
CORPORATE SOURCE:    Division of Basic Medical Sciences, Mercer University
                     School of Medicine, Macon, Georgia 31207, USA..
                     detmer.k@gain.mercer.edu
SOURCE:              Blood cells, molecules & diseases, (2000 Aug) Vol. 26, No.
                     4, pp. 360-72.
                     Journal code: 9509932. ISSN: 1079-9796.
PUB. COUNTRY:        United States
DOCUMENT TYPE:       Journal; Article; (JOURNAL ARTICLE)
                     (RESEARCH SUPPORT, NON-U.S. GOV'T)
LANGUAGE:            English
FILE SEGMENT:        Priority Journals
OTHER SOURCE:       GENBANK-AF130867
ENTRY MONTH:         200012
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ENTRY DATE: Entered STN: 22 Mar 2001
Last Updated on STN: 22 Mar 2001
Entered Medline: 22 Dec 2000

AB Adult hematopoietic differentiation is a developmental process that employs many of the same molecular mechanisms as embryogenesis. To explore the possibility that hedgehog signaling is involved in the control of hematopoietic differentiation, we screened a panel of human leukemia cell lines for the expression of Patched1 and Smoothened, the receptor and coreceptor for hedgehog ligands. Expression was found in multiple cell lines, and Patched1 expression was detected in normal marrow. Induction of myeloid differentiation in cell lines downregulated expression of both genes. When normal marrow mononuclear cells were grown in semisolid medium in the presence of 10 microM cyclopamine, development of colonies of granulocytic/monocytic lineage was unaffected in terms of both number and morphology. The number of erythroid colonies, however, was significantly reduced ($P < 0.01$). Furthermore, hemoglobinization was substantially delayed relative to controls in those erythroid colonies that did form. Incubation of hematopoietic progenitors with Shh-N and GM-CSF resulted in increased granulocyte/monocyte colonies ($P < 0.01$); the increase was blocked by cyclopamine. Incubation of hematopoietic progenitors with Shh-N and stem cell factor resulted in larger erythroid colonies. These results suggest that elements of the hedgehog signaling pathway are involved in the control of hematopoietic differentiation. Copyright 2000 Academic Press.

L3 ANSWER 3 OF 9 MEDLINE on STN
ACCESSION NUMBER: 2000465705 MEDLINE Full-text
DOCUMENT NUMBER: PubMed ID: 11021632
TITLE: Genetic and teratogenic approaches to craniofacial development.
AUTHOR: Young D L; Schneider R A; Hu D; Helms J A
CORPORATE SOURCE: Department of Orthopaedic Surgery, School of Medicine, University of California at San Francisco, 94143-0514, USA.
SOURCE: Critical reviews in oral biology and medicine : an official publication of the American Association of Oral Biologists, (2000) Vol. 11, No. 3, pp. 304-17. Ref: 121
Journal code: 9009999. ISSN: 1045-4411.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
(RESEARCH SUPPORT, NON-U.S. GOV'T)
(RESEARCH SUPPORT, U.S. GOV'T, P.H.S.)
General Review; (REVIEW)
LANGUAGE: English
FILE SEGMENT: Dental Journals; Priority Journals
ENTRY MONTH: 200101
ENTRY DATE: Entered STN: 22 Mar 2001
Last Updated on STN: 22 Mar 2001
Entered Medline: 4 Jan 2001

AB Craniofacial malformations are the most common birth defects that occur in humans, with facial clefting representing the majority of these defects. Facial clefts can arise at any stage of development due to perturbations that alter the extracellular matrix as well as affect the patterning, migration, proliferation, and differentiation of cells. In this review, we focus on recent advances in the understanding of the developmental basis for facial clefting through the analysis of the effects of gene disruption experiments and treatments with teratogens in both chickens and mice. Specifically, we analyze the results of disruptions to genes such as Sonic hedgehog (Shh), epidermal growth factor receptor (EGFR), Distal-less (Dlx), and transforming growth factor beta 3 (TGFbeta3). We also describe the effects that teratogens such as retinoic acid, jervine, and cyclopamine have on facial clefting and

```
      discuss mechanisms for their action.  In addition to providing insight into
      the bases for abnormal craniofacial growth, genetic and teratogenic techniques
      are powerful tools for understanding the normal developmental processes that
      generate and pattern the face.


L3   ANSWER 4 OF 9     MEDLINE on STN
ACCESSION NUMBER:    2000214854     MEDLINE  Full-text
DOCUMENT NUMBER:     PubMed ID: 10751185
TITLE:               The concentric structure of the developing gut is regulated
                     by Sonic hedgehog derived from endodermal epithelium.
AUTHOR:              Sukegawa A; Narita T; Kameda T; Saitoh K; Nohno T; Iba H;
                     Yasugi S; Fukuda K
CORPORATE SOURCE:    Department of Biology, Tokyo Metropolitan University,
                     Hachiohji, Tokyo, Japan.. kokko@comp.metro-u.ac.jp
SOURCE:              Development (Cambridge, England), (2000 May) Vol. 127, No.
                     9, pp. 1971-80.
                     Journal code: 8701744. ISSN: 0950-1991.
PUB. COUNTRY:        ENGLAND: United Kingdom
DOCUMENT TYPE:       Journal; Article; (JOURNAL ARTICLE)
                     (RESEARCH SUPPORT, NON-U.S. GOV'T)
LANGUAGE:            English
FILE SEGMENT:        Priority Journals
ENTRY MONTH:         200006
ENTRY DATE:          Entered STN: 22 Jun 2000
                     Last Updated on STN: 22 Jun 2000
                     Entered Medline: 15 Jun 2000
AB    The embryonic gut of vertebrates consists of endodermal epithelium,
      surrounding mesenchyme derived from splanchnic mesoderm and enteric neuronal
      components derived from neural crest cells.  During gut organogenesis, the
      mesenchyme differentiates into distinct concentric layers around the
      endodermal epithelium forming the lamina propria, muscularis mucosae,
      submucosa and lamina muscularis (the smooth muscle layer).  The smooth muscle
      layer and enteric plexus are formed at the outermost part of the gut, always
      some distance away from the epithelium. How this topographical organization of
      gut mesenchyme is established is largely unknown.  Here we show the following:
      (1) Endodermal epithelium inhibits differentiation of smooth muscle and
      enteric neurons in adjacent mesenchyme. (2) Endodermal epithelium activates
      expression of patched and BMP4 in adjacent non-smooth muscle mesenchyme, which
      later differentiates into the lamina propria and submucosa. (3) Sonic hedgehog
      (Shh) is expressed in endodermal epithelium and disruption of Shh-signaling by
      cyclopamine induces differentiation of smooth muscle and a large number of
      neurons even in the area adjacent to epithelium. (4) Shh can mimic the effect
      of endodermal epithelium on the concentric stratification of the gut.  Taken
      together, these data suggest that endoderm-derived Shh is responsible for the
      patterning across the radial axis of the gut through induction of inner
      components and inhibition of outer components, such as smooth muscle and
      enteric neurons.


L3   ANSWER 5 OF 9     MEDLINE on STN
ACCESSION NUMBER:    1999102111     MEDLINE  Full-text
DOCUMENT NUMBER:     PubMed ID: 9882493
TITLE:               Essential role for Sonic hedgehog during hair follicle
                     morphogenesis.
AUTHOR:              Chiang C; Swan R Z; Grachtchouk M; Bolinger M; Litingtung
                     Y; Robertson E K; Cooper M K; Gaffield W; Westphal H;
                     Beachy P A; Dlugosz A A
CORPORATE SOURCE:    Laboratory of Mammalian Genes and Development, National
                     Institutes of Health, Bethesda, Maryland, 20892, USA.
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SOURCE: Developmental biology, (1999 Jan 1) Vol. 205, No. 1, pp. 1-9.
Journal code: 0372762. ISSN: 0012-1606.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199902
ENTRY DATE: Entered STN: 23 Feb 1999
Last Updated on STN: 23 Feb 1999
Entered Medline: 5 Feb 1999

AB The hair follicle is a source of epithelial stem cells and site of origin for several types of skin tumors. Although it is clear that follicles arise by way of a series of inductive tissue interactions, identification of the signaling molecules driving this process remains a major challenge in skin biology. In this study we report an obligatory role for the secreted morphogen Sonic hedgehog (Shh) during hair follicle development. Hair germs comprising epidermal placodes and associated dermal condensates were detected in both control and Shh -/- embryos, but progression through subsequent stages of follicle development was blocked in mutant skin. The expression of Gli1 and Ptc1 was reduced in Shh -/- dermal condensates and they failed to evolve into hair follicle papillae, suggesting that the adjacent mesenchyme is a critical target for placode-derived Shh. Despite the profound inhibition of hair follicle morphogenesis, late-stage follicle differentiation markers were detected in Shh -/- skin grafts, as well as cultured vibrissa explants treated with cyclopamine to block Shh signaling. Our findings reveal an essential role for Shh during hair follicle morphogenesis, where it is required for normal advancement beyond the hair germ stage of development. Copyright 1999 Academic Press.

L3 ANSWER 6 OF 9 MEDLINE on STN
ACCESSION NUMBER: 1999007262 MEDLINE Full-text
DOCUMENT NUMBER: PubMed ID: 9789036
TITLE: Pancreas development is promoted by cyclopamine, a hedgehog signaling inhibitor.
AUTHOR: Kim S K; Melton D A
CORPORATE SOURCE: Howard Hughes Medical Institute and Department of Molecular and Cellular Biology, Harvard University, Cambridge, MA 02138, USA.. seungkim@cmgm.stanford.edu
SOURCE: Proceedings of the National Academy of Sciences of the United States of America, (1998 Oct 27) Vol. 95, No. 22, pp. 13036-41.
Journal code: 7505876. ISSN: 0027-8424.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
(RESEARCH SUPPORT, NON-U.S. GOV'T)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199811
ENTRY DATE: Entered STN: 6 Jan 1999
Last Updated on STN: 6 Jan 1999
Entered Medline: 24 Nov 1998

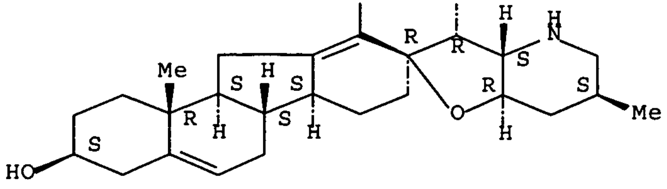
AB Exposure to cyclopamine, a steroid alkaloid that blocks Sonic hedgehog (Shh) signaling, promotes pancreatic expansion in embryonic chicks. Heterotopic development of pancreatic endocrine and exocrine structures occurs in regions adjacent to the pancreas including stomach and duodenum, and insulin-producing islets in the pancreas are enlarged. The homeodomain transcription factor PDX1, required for pancreas development, is expressed broadly in the posterior foregut but pancreas development normally initiates only in a restricted region of PDX1-expressing posterior foregut where endodermal Shh expression is repressed. The results suggests that cyclopamine expands the endodermal region where Shh signaling does not occur, resulting in pancreatic differentiation in a larger region of PDX1-expressing foregut endoderm. Cyclopamine reveals the capacity of a broad region of the posterior embryonic foregut to form pancreatic cells and provides a means for expanding embryonic pancreas development.

L3 ANSWER 7 OF 9 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1998:711779 CAPLUS Full-text
DOCUMENT NUMBER: 130:77262
TITLE: Pancreas development is promoted by cyclopamine, a Hedgehog signaling inhibitor
AUTHOR(S): Kim, Seung K.; Melton, Douglas A.
CORPORATE SOURCE: Howard Hughes Medical Institute and Department of Molecular and Cellular Biology, Harvard University; Cambridge, MA, 02138, USA
SOURCE: Proceedings of the National Academy of Sciences of the United States of America (1998), 95(22), 13036-13041
CODEN: PNASA6; ISSN: 0027-8424
PUBLISHER: National Academy of Sciences
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Exposure to cyclopamine, a steroid alkaloid that blocks Sonic hedgehog (Shh) signaling, promotes pancreatic expansion in embryonic chicks. Heterotopic development of pancreatic endocrine and exocrine structures occurs in regions adjacent to the pancreas including the stomach and duodenum, and insulin-producing islets in the pancreas are enlarged. The homeodomain transcription factor PDX1, required for pancreas development, is expressed broadly in the posterior foregut but pancreas development normally initiates only in a restricted region of PDX1-expressing posterior foregut where endodermal Shh expression is repressed. The results suggest that cyclopamine expands the endodermal region where Shh signaling does not occur, resulting in pancreatic differentiation in a larger region of PDX1-expressing foregut endoderm. Cyclopamine reveals the capacity of a broad region of the posterior embryonic foregut to form pancreatic cells and provides a means for expanding embryonic pancreas development.

IT 4449-51-8, Cyclopamine
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(pancreas development promotion by cyclopamine)
RN 4449-51-8 CAPLUS
CN Spiro[9H-benzo[a]fluorene-9,2'(3'H)-furo[3,2-b]pyridin]-3-ol, 1,2,3,3'a,4,4',5',6,6',6a,6b,7,7',7'a,8,11,11a,11b-octadecahydro-3',6',10,11b-tetramethyl-, (2'R,3S,3'R,3'aS,6'S,6aS,6bS,7'aR,11aS,11bR)-(9CI) (CA INDEX NAME)

Absolute stereochemistry.



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REFERENCE COUNT:          43     THERE ARE 43 CITED REFERENCES AVAILABLE FOR THIS
                                 RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3   ANSWER 8 OF 9  USPATFULL on STN
ACCESSION NUMBER:        2001:218003  USPATFULL  Full-text
TITLE:                   Stem cells of the islets of langerhans and their use in
                         treating diabetes mellitus
INVENTOR(S):             Habener, Joel E., Newton Center, MA, United States
                         Zulewski, Henryk, Geneva, Switzerland
                         Abraham, Elizabeth J., Quincy, MA, United States
                         Thomas, Melissa K., Boston, MA, United States
                         Vallejo, Mario, Madrid, Spain

                              NUMBER        KIND    DATE
                         ---------------- ------ --------
PATENT INFORMATION:      US 2001046489       A1   20011129
APPLICATION INFO.:       US 2000-731261      A1   20001206  (9)

                                NUMBER       DATE
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PRIORITY INFORMATION:    US 1999-169082P    19991206 (60)
                         US 2000-215109P    20000628 (60)
                         US 2000-238880P    20001006 (60)
DOCUMENT TYPE:           Utility
FILE SEGMENT:            APPLICATION
LEGAL REPRESENTATIVE:    Kathleen M. Williams, Ph.D, Palmer & Dodge, LLP, One
                         Beacon Street, Boston, MA, 02108
NUMBER OF CLAIMS:        41
EXEMPLARY CLAIM:         1
NUMBER OF DRAWINGS:      19 Drawing Page(s)
LINE COUNT:              2114
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB       Methods and compositions are described for the treatment of type I insulin-
         dependent diabetes mellitus and other conditions using newly identified stem
         cells that are capable of differentiation into a variety of pancreatic islet
         cells, including insulin-producing beta cells, as well as hepatocytes.
         Nestin has been identified as a molecular marker for pancreatic stem cells,
         while cytokeratin-19 serves as a marker for a distinct class of islet ductal
         cells. Methods are described whereby nestin-positive stem cells can be
         isolated from pancreatic islets and cultured to obtain further stem cells or
         pseudo-islet like structures. Methods for ex vivo differentiation of the
         pancreatic stem cells are disclosed. Methods are described whereby
         pancreatic stem cells can be isolated, expanded, and transplanted into a
         patient in need thereof, either allogeneically, isogeneically or
         xenogenically, to provide replacement for lost or damaged insulin-secreting
         cells or other cells.


CAS INDEXING IS AVAILABLE FOR THIS PATENT.
IT   4449-51-8, Cyclopamine
        (isolation, culture, and transplantation of nestin-pos. pancreatic stem
        cells for diabetes treatment)
RN   4449-51-8  USPATFULL
CN   Spiro[9H-benzo[a]fluorene-9,2'(3'H)-furo[3,2-b]pyridin]-3-ol,
       1,2,3,3'a,4,4',5',6,6',6a,6b,7,7',7'a,8,11,11a,11b-octadecahydro-
       3',6',10,11b-tetramethyl-, (2'R,3S,3'R,3'aS,6'S,6aS,6bS,7'aR,11aS,11bR)-
       (9CI)  (CA INDEX NAME)
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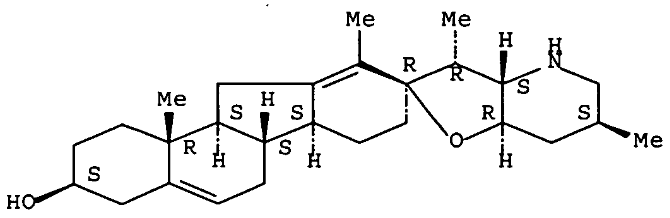
Absolute stereochemistry.



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L3   ANSWER 9 OF 9  USPATFULL on STN
ACCESSION NUMBER:        2001:158338  USPATFULL  Full-text
TITLE:                   Regulators of the hedgehog pathway, compositions and
                         uses related thereto
INVENTOR(S):             Dudek, Henryk, Wellesley, MA, United States
                         Ji, Benxiu, Sharon, MA, United States
PATENT ASSIGNEE(S):      Curis, Inc., Cambridge, MA, United States (U.S.
                         corporation)

                              NUMBER        KIND    DATE
                         ---------------- ------ --------
PATENT INFORMATION:      US 6291516        B1    20010918
APPLICATION INFO.:       US 1999-417564          19991014   (9)

                                NUMBER        DATE
                         ------------------ --------
PRIORITY INFORMATION:    US 1999-115642P    19990113 (60)
                         US 1999-119594P    19990210 (60)
                         US 1999-142124P    19990702 (60)
DOCUMENT TYPE:           Utility
FILE SEGMENT:            GRANTED
PRIMARY EXAMINER:        Krass, Frederick
LEGAL REPRESENTATIVE:    Vincent, Matthew P., Halstead, David P.Ropes & Gray
NUMBER OF CLAIMS:        16
EXEMPLARY CLAIM:         1
NUMBER OF DRAWINGS:      19 Drawing Figure(s); 19 Drawing Page(s)
LINE COUNT:              3730
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB       The present invention makes available methods and reagents for inhibiting
       aberrant growth states resulting from hedgehog gain-of-function, ptc loss-
       of-function or smoothened gain-of-function comprising contacting a cell with
       a compound, such as a polypeptide or small molecule in an amount sufficient
       to control the aberrant growth state, e.g., to agonize a normal ptc pathway
       or antagonize smoothened or hedgehog activity. The present invention further
       makes available methods and reagents for ameliorating the consequences of
       hedgehog loss-of-function, ptc gain-of-function, or smoothened loss-of-
       function comprising contacting a cell with a compound, such as a polypeptide
       or small molecule, in an amount sufficient to ameliorate the In certain
       embodiments, the subject compounds, e.g., a cAMP analog, adenylate cyclase
       agonist, or cAMP phosphodiesterase inhibitor, regulate cAMP levels, which in
       turn modulates activity of the hedgehog pathway.


CAS INDEXING IS AVAILABLE FOR THIS PATENT.
IT   4449-51-8, Cyclopamine
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        (regulation of the hedgehog pathway and smoothened gain-of-function by
        gene patched agonists)
RN    4449-51-8  USPATFULL
CN    Spiro[9H-benzo[a]fluorene-9,2'(3'H)-furo[3,2-b]pyridin]-3-ol,
        1,2,3,3'a,4,4',5',6,6',6a,6b,7,7',7'a,8,11,11a,11b-octadecahydro-
        3',6',10,11b-tetramethyl-, (2'R,3S,3'R,3'aS,6'S,6aS,6bS,7'aR,11aS,11bR)-
        (9CI)  (CA INDEX NAME)

       Absolute stereochemistry.
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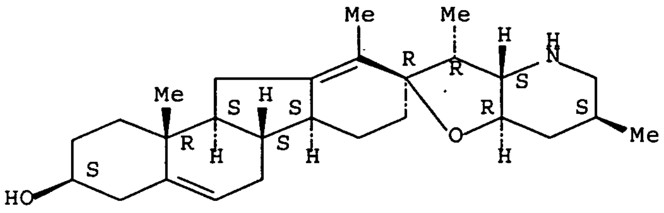

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=> s l1 and "hedgehog"
L4          264 L1 AND "HEDGEHOG"

=> s l4 not py>2001
L5           28 L4 NOT PY>2001

=> s l5 and "smoothened"
L6            6 L5 AND "SMOOTHENED"

=> d l6 1-6 ibib, abs

L6   ANSWER 1 OF 6     MEDLINE on STN
ACCESSION NUMBER:    2001069870     MEDLINE  Full-text
DOCUMENT NUMBER:     PubMed ID: 11118005
TITLE:               Hedgehog signaling regulation of insulin
                     production by pancreatic beta-cells.
AUTHOR:              Thomas M K; Rastalsky N; Lee J H; Habener J F
CORPORATE SOURCE:    Laboratory of Molecular Endocrinology, Massachusetts
                     General Hospital, Howard Hughes Medical Institute, Harvard
                     Medical School, Boston 02114, USA.
CONTRACT NUMBER:     DK30457 (NIDDK)
                     DK30834 (NIDDK)
                     DK55365 (NIDDK)
                     +
SOURCE:              Diabetes, (2000 Dec) Vol. 49, No. 12, pp. 2039-47.
                     Journal code: 0372763. ISSN: 0012-1797.
PUB. COUNTRY:        United States
DOCUMENT TYPE:       Journal; Article; (JOURNAL ARTICLE)
                     (RESEARCH SUPPORT, NON-U.S. GOV'T)
                     (RESEARCH SUPPORT, U.S. GOV'T, P.H.S.)
LANGUAGE:            English
FILE SEGMENT:        Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH:         200101
ENTRY DATE:          Entered STN: 22 Mar 2001
                     Last Updated on STN: 22 Mar 2001
                     Entered Medline: 4 Jan 2001
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AB Hedgehogs (Hhs) are intercellular signaling molecules that regulate tissue patterning in mammalian development. Mammalian Hhs include Sonic hedgehog (Shh), Indian hedgehog (Ihh), and Desert hedgehog (Dhh). The absence of Shh expression is required for the early development of the endocrine and exocrine pancreas, but whether Hh signaling functions in the fully developed adult endocrine pancreas is unknown. Here we report that Hhs Ihh and Dhh and their receptors patched (Ptc) and smoothened are expressed in the endocrine islets of Langerhans of the fully developed rat pancreas and in the clonal gamma-cell line INS-1. We demonstrate the coexpression of Ptc with insulin in beta-cells of mouse pancreatic islets, indicating that beta-cells are targets of active Hh signaling. The administration of cyclopamine, a Hh signaling inhibitor, decreases both insulin secretion from and insulin content of INS-1 cells. The effects of Hh signaling on insulin production occur at the transcriptional level because activation of Hh signal transduction by ectopic expression of Shh increases rat insulin I promoter activation in a dose-dependent manner in transient transfections of INS-1 and MIN6 beta-cell lines. In contrast, inhibition of Hh signaling with increasing concentrations of cyclopamine progressively reduces insulin promoter activity. Furthermore, the treatment of INS-1 cells with cyclopamine diminishes endogenous insulin mRNA expression. We propose that Hh signaling is not restricted to patterning in early pancreas development but also continues to signal in differentiated beta-cells of the endocrine pancreas in regulating insulin production. Thus, defective Hh signaling in the pancreas should be considered as a potential factor in the pathogenesis of type 2 diabetes.

L6 ANSWER 2 OF 6 MEDLINE on STN

ACCESSION NUMBER:	2001059467 MEDLINE Full-text
DOCUMENT NUMBER:	PubMed ID: 11042037
TITLE:	Erythroid differentiation in vitro is blocked by cyclopamine, an inhibitor of hedgehog signaling.
AUTHOR:	Detmer K; Walker A N; Jenkins T M; Steele T A; Dannawi H
CORPORATE SOURCE:	Division of Basic Medical Sciences, Mercer University School of Medicine, Macon, Georgia 31207, USA.. detmer.k@gain.mercer.edu
SOURCE:	Blood cells, molecules & diseases, (2000 Aug) Vol. 26, No. 4, pp. 360-72. Journal code: 9509932. ISSN: 1079-9796.
PUB. COUNTRY:	United States
DOCUMENT TYPE:	Journal; Article; (JOURNAL ARTICLE) (RESEARCH SUPPORT, NON-U.S. GOV'T)
LANGUAGE:	English
FILE SEGMENT:	Priority Journals
OTHER SOURCE:	GENBANK-AF130867
ENTRY MONTH:	200012
ENTRY DATE:	Entered STN: 22 Mar 2001 Last Updated on STN: 22 Mar 2001 Entered Medline: 22 Dec 2000

AB Adult hematopoietic differentiation is a developmental process that employs many of the same molecular mechanisms as embryogenesis. To explore the possibility that hedgehog signaling is involved in the control of hematopoietic differentiation, we screened a panel of human leukemia cell lines for the expression of Patched1 and Smoothened , the receptor and coreceptor for hedgehog ligands. Expression was found in multiple cell lines, and Patched1 expression was detected in normal marrow. Induction of myeloid differentiation in cell lines downregulated expression of both genes. When normal marrow mononuclear cells were grown in semisolid medium in the presence of 10 microM cyclopamine, development of colonies of granulocytic/monocytic lineage was unaffected in terms of both number and morphology. The number of erythroid colonies, however, was significantly reduced ($P < 0.01$).

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          Furthermore, hemoglobinization was substantially delayed relative to controls
          in those erythroid colonies that did form.  Incubation of hematopoietic
          progenitors with Shh-N and GM-CSF resulted in increased granulocyte/monocyte
          colonies (P < 0.01); the increase was blocked by cyclopamine.  Incubation of
          hematopoietic progenitors with Shh-N and stem cell factor resulted in larger
          erythroid colonies.  These results suggest that elements of the hedgehog
          signaling pathway are involved in the control of hematopoietic
          differentiation. Copyright 2000 Academic Press.


L6   ANSWER 3 OF 6     MEDLINE on STN
ACCESSION NUMBER:    2000439367     MEDLINE  Full-text
DOCUMENT NUMBER:     PubMed ID: 10984056
TITLE:               Effects of oncogenic mutations in Smoothened and
                     Patched can be reversed by cyclopamine.
AUTHOR:              Taipale J; Chen J K; Cooper M K; Wang B; Mann R K;
                     Milenkovic L; Scott M P; Beachy P A
CORPORATE SOURCE:    Department of Molecular Biology and Genetics, Howard Hughes
                     Medical Institute, The Johns Hopkins University School of
                     Medicine, Baltimore, Maryland 21205, USA.
SOURCE:              Nature, (2000 Aug 31) Vol. 406, No. 6799, pp. 1005-9.
                     Journal code: 0410462. ISSN: 0028-0836.
PUB. COUNTRY:        ENGLAND: United Kingdom
DOCUMENT TYPE:       Journal; Article; (JOURNAL ARTICLE)
                     (RESEARCH SUPPORT, NON-U.S. GOV'T)
LANGUAGE:            English
FILE SEGMENT:        Priority Journals
ENTRY MONTH:         200009
ENTRY DATE:          Entered STN: 28 Sep 2000
                     Last Updated on STN: 28 Sep 2000
                     Entered Medline: 21 Sep 2000
AB    Basal cell carcinoma, medulloblastoma, rhabdomyosarcoma and other human
      tumours are associated with mutations that activate the proto-oncogene
      Smoothened (SMO) or that inactivate the tumour suppressor Patched (PTCH).
      Smoothened and Patched mediate the cellular response to the Hedgehog (Hh)
      secreted protein signal, and oncogenic mutations affecting these proteins
      cause excess activity of the Hh response pathway.  Here we show that the
      plant-derived teratogen cyclopamine, which inhibits the Hh response, is a
      potential 'mechanism-based' therapeutic agent for treatment of these tumours.
      We show that cyclopamine or synthetic derivatives with improved potency block
      activation of the Hh response pathway and abnormal cell growth associated with
      both types of oncogenic mutation.  Our results also indicate that cyclopamine
      may act by influencing the balance between active and inactive forms of
      Smoothened.


L6   ANSWER 4 OF 6  CAPLUS  COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER:         2000:637045  CAPLUS  Full-text
DOCUMENT NUMBER:          133:344307
TITLE:                    Effects of oncogenic mutations in Smoothened
                          and Patched can be reversed by cyclopamine
AUTHOR(S):                Taipale, Jussl; Chen, James K.; Cooper, Michael K.;
                          Wang, Baolin; Mann, Randall K.; Milenkovic, Ljiljana;
                          Scotts, Matthew P.; Beachy, Philip A.
CORPORATE SOURCE:         Department of Molecular Biology and Genetics, The
                          Johns Hopkins University School of Medicine,
                          Baltimore, MD, 21205, USA
SOURCE:                   Nature (London) (2000), 406(6799), 1005-1009
                          CODEN: NATUAS; ISSN: 0028-0836
PUBLISHER:                Nature Publishing Group
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DOCUMENT TYPE:          Journal
LANGUAGE:               English
AB   Basal cell carcinoma, medulloblastoma, rhabdomyosarcoma and other human tumors
     are associated with mutations that activate the proto-oncogene Smoothened
     (SMO) or that inactivate the tumor suppressor Patched (PTCH).  Smoothened and
     Patched mediate the cellular response to the Hedgehog (Hh) secreted protein
     signal, and oncogenic mutations affecting these proteins cause excess activity
     of the Hh response pathway.  Here we show that the plant-derived teratogen
     cyclopamine, which inhibits the Hh response, is a potential 'mechanism-based'
     therapeutic agent for treatment of these tumors.  We show that cyclopamine or
     synthetic derivs. with improved potency block activation of the Hh response
     pathway and abnormal cell growth associated with both types of oncogenic
     mutation.  Our results also indicate that cyclopamine may act by influencing
     the balance between active and inactive forms of Smoothened.
REFERENCE COUNT:        29    THERE ARE 29 CITED REFERENCES AVAILABLE FOR THIS
                              RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6   ANSWER 5 OF 6  USPATFULL on STN
ACCESSION NUMBER:       2001:218003  USPATFULL  Full-text
TITLE:                  Stem cells of the islets of langerhans and their use in
                        treating diabetes mellitus
INVENTOR(S):            Habener, Joel E., Newton Center, MA, United States
                        Zulewski, Henryk, Geneva, Switzerland
                        Abraham, Elizabeth J., Quincy, MA, United States
                        Thomas, Melissa K., Boston, MA, United States
                        Vallejo, Mario, Madrid, Spain

                             NUMBER        KIND    DATE
                        --------------- ------ --------
PATENT INFORMATION:     US 2001046489      A1   20011129
APPLICATION INFO.:      US 2000-731261     A1   20001206  (9)

                               NUMBER        DATE
                        ------------------ --------
PRIORITY INFORMATION:   US 1999-169082P    19991206 (60)
                        US 2000-215109P    20000628 (60)
                        US 2000-238880P    20001006 (60)
DOCUMENT TYPE:          Utility
FILE SEGMENT:           APPLICATION
LEGAL REPRESENTATIVE:   Kathleen M. Williams, Ph.D, Palmer & Dodge, LLP, One
                        Beacon Street, Boston, MA, 02108
NUMBER OF CLAIMS:       41
EXEMPLARY CLAIM:        1
NUMBER OF DRAWINGS:     19 Drawing Page(s)
LINE COUNT:             2114
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB      Methods and compositions are described for the treatment of type I insulin-
        dependent diabetes mellitus and other conditions using newly identified stem
        cells that are capable of differentiation into a variety of pancreatic islet
        cells, including insulin-producing beta cells, as well as hepatocytes.
        Nestin has been identified as a molecular marker for pancreatic stem cells,
        while cytokeratin-19 serves as a marker for a distinct class of islet ductal
        cells. Methods are described whereby nestin-positive stem cells can be
        isolated from pancreatic islets and cultured to obtain further stem cells or
        pseudo-islet like structures. Methods for ex vivo differentiation of the
        pancreatic stem cells are disclosed. Methods are described whereby
        pancreatic stem cells can be isolated, expanded, and transplanted into a
        patient in need thereof, either allogeneically, isogeneically or
        xenogenically, to provide replacement for lost or damaged insulin-secreting
        cells or other cells.
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CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L6   ANSWER 6 OF 6  USPATFULL on STN
ACCESSION NUMBER:        2001:158338  USPATFULL  Full-text
TITLE:                   Regulators of the hedgehog pathway,
                         compositions and uses related thereto
INVENTOR(S):             Dudek, Henryk, Wellesley, MA, United States
                         Ji, Benxiu, Sharon, MA, United States
PATENT ASSIGNEE(S):      Curis, Inc., Cambridge, MA, United States (U.S.
                         corporation)

                              NUMBER       KIND    DATE
                         ---------------- ------ --------
PATENT INFORMATION:      US 6291516         B1   20010918
APPLICATION INFO.:       US 1999-417564          19991014  (9)

                                NUMBER        DATE
                         ----------------- --------
PRIORITY INFORMATION:    US 1999-115642P    19990113 (60)
                         US 1999-119594P    19990210 (60)
                         US 1999-142124P    19990702 (60)
DOCUMENT TYPE:           Utility
FILE SEGMENT:            GRANTED
PRIMARY EXAMINER:        Krass, Frederick
LEGAL REPRESENTATIVE:    Vincent, Matthew P., Halstead, David P.Ropes & Gray
NUMBER OF CLAIMS:        16
EXEMPLARY CLAIM:         1
NUMBER OF DRAWINGS:      19 Drawing Figure(s); 19 Drawing Page(s)
LINE COUNT:              3730
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB       The present invention makes available methods and reagents for inhibiting
         aberrant growth states resulting from hedgehog gain-of-function, ptc loss-
         of-function or smoothened gain-of-function comprising contacting a cell with
         a compound, such as a polypeptide or small molecule in an amount sufficient
         to control the aberrant growth state, e.g., to agonize a normal ptc pathway
         or antagonize smoothened or hedgehog activity. The present invention further
         makes available methods and reagents for ameliorating the consequences of
         hedgehog loss-of-function, ptc gain-of-function, or smoothened loss-of-
         function comprising contacting a cell with a compound, such as a polypeptide
         or small molecule, in an amount sufficient to ameliorate the In certain
         embodiments, the subject compounds, e.g., a cAMP analog, adenylate cyclase
         agonist, or cAMP phosphodiesterase inhibitor, regulate cAMP levels, which in
         turn modulates activity of the hedgehog pathway.


CAS INDEXING IS AVAILABLE FOR THIS PATENT.


=> d his

     (FILE 'HOME' ENTERED AT 13:23:36 ON 03 APR 2007)

     FILE 'REGISTRY' ENTERED AT 13:23:49 ON 03 APR 2007
L1             6 S "CYCLOPAMINE"

     FILE 'MEDLINE, CAPLUS, WPIDS, USPATFULL' ENTERED AT 13:24:26 ON 03 APR
     2007
L2           154 S L1 AND ("DIFFERENTIATION" OR "APOPTOSIS")
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L3             9 S L2 NOT PY>2001
L4           264 S L1 AND "HEDGEHOG"
L5            28 S L4 NOT PY>2001
L6             6 S L5 AND "SMOOTHENED"

=>

---Logging off of STN---



=>
Executing the logoff script...


=> LOG Y

COST IN U.S. DOLLARS                                 SINCE FILE      TOTAL
                                                          ENTRY    SESSION
FULL ESTIMATED COST                                       53.16      58.77

DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)           SINCE FILE      TOTAL
                                                          ENTRY    SESSION
CA SUBSCRIBER PRICE                                       -1.56      -1.56

STN INTERNATIONAL LOGOFF AT 13:28:56 ON 03 APR 2007
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